Hypogonadism as a possible link between metabolic diseases and erectile dysfunction in aging men

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Review

Hypogonadism as a possible link between metabolic diseases and erectile dysfunction in aging men

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ABSTRACT

There is evidence demonstrating that sexual complaints represent the most specific symptoms associated with late onset hypogonadism, while central obesity is the most specific sign. In obese men, hypogonadism can further worsen the metabolic profile and increase abdominal fat. In addition, although hypogonadism can exacerbate obesity-associated erectile dysfunction (ED), recent data suggest that a direct contribution of fat-derived factors could be hypothesized. In particular, an animal model recently documented that fat accumulation induces several hepatic pro-inflammatory genes closely linked to corpora cavernosa endothelial dysfunction. Lifestyle modifications and weight loss are the first steps in the treatment of ED patients with obesity or metabolic diseases. In symptomatic hypogonadal men with metabolic impairment and obesity, combining the effect of testosterone substitution with lifestyle modifications could result in better outcomes.

Key words: Erectile dysfunction, Metabolic syndrome, Obesity, Testosterone

INTRODUCTION

Several population-based surveys have documented that in men testosterone (T) levels progressively decline with age.[1-5] In particular, according to the European Male Aging Study (EMAS), a survey of more than 3400 community-dwelling, middle-aged and older men, after the third decade T decreases by 0.4–2% per year.[5] The specific mechanisms underlying this phenomenon have not been completely clarified but age-related associated morbidities rather than aging per se seem to play a major role.[5,6]

Different T thresholds have been proposed for the biochemical definition of low T[7,8] in aging men, also known as late onset hypogonadism (LOH). The most widely shared consensus[7,8] is that T substitution may be beneficial when circulating total T is below 8 nmol/L (231 ng/dL) in two measurements. Moreover, there is also general agreement that a total T level above 12 nmol/L (346 ng/dL) does not require substitution. There is in addition a consensus that a reduction of T is not sufficient to define a clinically relevant hypogonadal state, especially in the "gray area", with circulating T between 8 and 12 nmol/L.[7,8]

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Hence, to define LOH, specific hypogonadism-related symptoms and signs should also be present.[7-10] Data from the EMAS survey clearly demonstrated that sexual symptoms, in particular low libido and reduced spontaneous and sex-related erections, represent the most specific symptoms associated with low T (total T level of less than 11 nmol/L and a free T (FT) level of less than 0.225 nmol/L).[11]

In line with this evidence, in male subjects consulting for sexual dysfunction, in contrast to other forms of male hypogonadism, LOH is a relatively common condition. Figure 1 shows the prevalence of symptomatic LOH in the general population of Florence, one of the participating centers in the EMAS survey, according to age intervals. By using the strict EMAS criteria, the prevalence of LOH in Florence increases from being quite an unusual condition in the younger age groups to more than 3% in the oldest one. In the same figure, using the same diagnostic criteria, the prevalence of LOH in subjects seeking medical care at an andrology unit for sexual dysfunction at the University of Florence (UNIFI) - hence from the same geographic area - is reported. It is evident that in subjects complaining of sexual dysfunction LOH is 5 times more prevalent than in the general population.

A large body of evidence has demonstrated that although sexual complaints represent the most specific symptoms associated with LOH, central obesity is the most specific sign.[7,8,12-14] Obesity (and in particular central obesity-related complications) is also a well-recognized risk factor for erectile dysfunction.[15,16] Although obesity related metabolic and cardiovascular (CV) complications have been proposed as playing a major pathogenetic role, recent studies have also suggested a direct contribution of several visceral fat-derived factors including chemokines, cytokines and hormones in the pathogenesis of ED[17] (see for review 15,16).

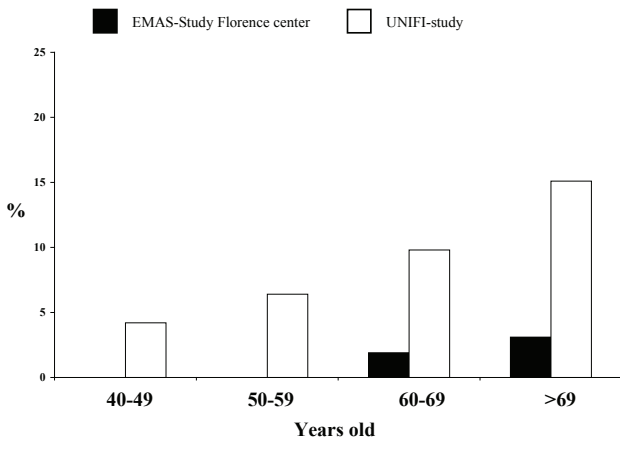

Figure 1. Prevalence of hypogonadism according to the European Male Aging Study (EMAS) criteria (11) in Florentine subjects of the EMAS survey (n=433) and in a consecutive series of (n=3293) output-patients receiving medical care for sexual dysfunction between 2000-2011 at our center (UNIFI study; 10).

In this review, we will analyze in depth the relationship between obesity, its metabolic complications and male hypogonadism (HG), and their contribution to the pathogenesis of ED.

METABOLIC IMPAIRMENT AND HYPOGONADISM: A BIDIRECTIONAL LINK CONTRIBUTING TO ED

Clinical evidence

The association between LOH, obesity, metabolic syndrome (MetS), insulin resistance and type 2 diabetes (T2DM) is well known.[7,8,14,18,19] In two independent meta-analyses of the available evidence, we have reported that subjects with MetS and T2DM have significantly reduced T levels (about 3 nmol/l lower).[21,22] These data were more recently confirmed in subjects with MetS by Brand et al[23] and Zumoff et al,[24] and we ourselves[25] previously showed an inverse correlation between body mass index (BMI) and both total and free T. In addition, this feature was not associated with an adequate increase in luteinizing hormone (LH) levels, suggesting the presence of obesity-related pituitary impairment response (Figure 2). In accord with this data morbidly obese men indicate that LH levels and pulse amplitude were attenuated when compared to normal weight controls.[26,27] Similarly, a recent study indicates that in subjects with T2DM there is a decreased gonadotropin-releasing hormone (GnRH) pulsatility without significant change in pituitary sensitivity to GnRH or in testis sensitivity to human chorionic gonadotropin.[28]

Longitudinal analysis of data suggested, however, the presence of a bidirectional link between obesity and low T. In fact, although low T at baseline increased

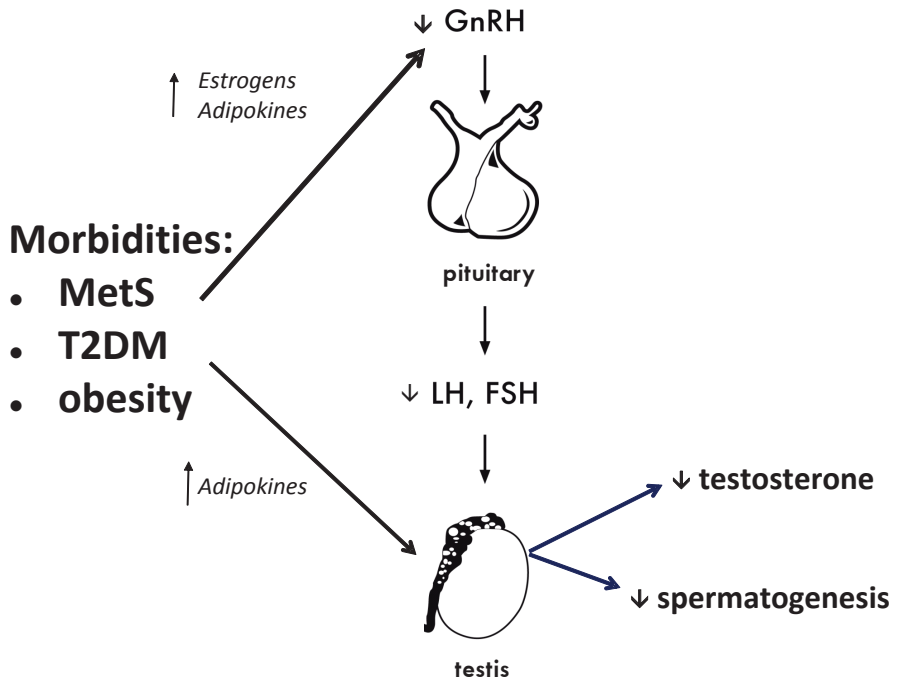

Figure 2. Proposed interactions between increased visceral fat and hypogonadism. MetS: metabolic syndrome; T2DM: type 2 diabetes mellitus; LH: luteinizing hormone; FSH: follicle stimulating hormone. GnRH: gonadotropin releasing hormone; T: testosterone.

the risk of T2DM and MetS at follow up[21-23] the opposite phenomenon has also been documented.[14,18] Similarly, longitudinal data from the EMAS survey showed that weight gain was progressively associated with a decline in T levels, whereas weight loss was proportionately associated with increases in T.[29]

By comparing the prevalence of endocrine abnormalities in two different cohorts from the general (Florentine spin-off of the EMAS cohort; n = 202) and the symptomatic populations of Florence (a series of n=3847 patients attending our clinic for ED; UNIFI cohort), we recently reported that secondary hypogonadism as well as central obesity (waist >102 cm), impaired fasting glucose (IFG) and T2DM were more often detected in UNIFI patients when compared to the EMAS cohort.[30] Hence, our data confirm that ED populations represent a cohort of subjects with increased incidence of metabolic abnormalities and hypogonadism. It is conceivable that central obesity-associated hypogonadism might partially justify this association. However, our analyses indicated that the association between central obesity and ED in the UNIFI cohort was confirmed even after the adjustment for T levels and BMI, suggesting a direct role of central obesity in the pathogenies of ED. In line with this hypothesis, we previously reported that the association between ED and central obesity was independent of known obesity-associated comorbidities (including hypogonadism) and was more strongly linked to an organic than to psychological and relational problems.[15] Similar results were reported by the EMAS survey.[31] Longitudinal data confirmed that obesity and central obesity at baseline were the most important predictors for the development of secondary hypogonadism at follow up.[31] However, incident secondary hypogonadism was associated, independently of BMI, comorbidities and lifestyle, with new or worsening sexual symptoms but not physical or psychological ones.[31]

Preclinical evidence

The specific pathogenetic mechanisms linking LOH with obesity and metabolic derangements appear to be complex and are not as yet completely understood (Figure 2). The presence of a hypothalamus-pituitary pathway impairment seems to represent the key feature. Several adipokines (e.g. leptin), cytokines (e.g. tumor necrosis factor-α; TNFα) and gastrointestinal hormones (e.g. ghrelin), along with increased estrogen

production by the expanded fat deposits, have been suggested as causing the gonadotropin failure.[14,32-34] One of the most intriguing working hypotheses is related to the role played by estrogens (Figure 2). The increased estrogen levels, which characterize obesity, might in turn have a negative effect on both the hypothalamus and the pituitary, leading to decreased LH secretion.[14,32-34] Accordingly, the use of the aromatase inhibitor letrozole can restore T levels and increase LH levels in severely obese hypogonadal men.[35] Similarly, body weight loss, obtained through either lifestyle or bariatric intervention, is associated with a fall in estrogen levels and with a rise in gonadotropins and T.[36] However, the role of estrogens in reducing GnRH-gonadotropin secretion has not been confirmed in obese diabetic[23] and non-diabetic men.[6] Hence, besides estrogens, other fat-associated factors have been proposed as a link between obesity and reproductive axis disorders (Figure 2). In fact, obesity may cause peripheral and central insulin resistance, pro-inflammatory cytokine production (TNFα and interleukin-6, IL-6) from adipocytes and central nervous system endocannabinoid release that can induce down-regulation of hypothalamic function.[14,31] In an animal model of MetS, we previously reported that increased visceral fat and the overall MetS condition, and in particular the related altered glucose and lipid metabolism, were associated with hypothalamic inflammation and derangement in the neuron network controlling GnRH release.[32,33,38] In addition, it is possible that peripheral metabolic derangements, such as those clustered in the MetS, signal to the hypothalamus via increased local inflammation and via a glucose-centered down-regulation of the neuronal network controlling GnRH release. In fact, recent findings demonstrated that a subpopulation of GnRH neurons projects dendrites into regions outside the blood brain barrier, where they may directly sense molecules circulating in the bloodstream.[39] Using a well characterized cellular model, we identified a direct inhibitory action of increasing glucose concentrations on human fetal GnRH-secreting neurons, the FNC-B4 cells.[32] In line with this hypothesis, we recently reported that in subjects with ED almost ¾ of cases of the unknown causes of hypogonadism can be attributed to metabolic abnormalities including obesity and MetS.[40]

Furthermore, established hypogonadism might also worsen obesity. In vitro studies indicate that androgens inhibit adipogenic differentiation of mouse or human preadipocytes (rPAD) through an androgen receptor (AR)-mediated pathway.[41,42] In addition, we demonstrated that high-fat-diet (HFD)-induced hypogonadism in rabbits determines the impairment of several cellular abnormalities in rPAD, including a reduced ability of triglyceride synthesis, glucose uptake, protein kinase B (AKT) phosphorylation and glucose transporter type 4 (GLUT4) membrane translocation, as well as by the reduced expression of adipogenic genes.[43,44]

Despite the specific mechanisms linking obesity and hypogonadism, our experimental data support the view of a direct role of obesity in the pathogenesis of ED. In fact, the strong association between visceral adiposity and impaired acetylcholine-induced relaxation in the corpora cavernosa (CC) was not explained by any metabolic or hormonal alteration considered.[15] In a further study by our group,[17] we demonstrated that in an animal model diet-induced visceral-fat accumulation was associated with nonalcoholic steatohepatitis (NASH) and that several hepatic pro-inflammatory genes were closely linked to CC endothelial dysfunction (acetylcholine responsiveness). In particular, we proposed that NASH plays an active role in the pathogenesis of ED through TNFα.[17]

Interventional evidence

Lifestyle modifications

According to all recommendations, lifestyle modifications should be the usual first-line approach for all patients. In fact, there is a good deal of evidence documenting that in individuals at risk, intensive lifestyle interventions, along with nutritional counseling and physical activity, are able to reduce weight and insulin resistance, thus preventing the progression of obesity to other diseases, such as overt diabetes and CV disease.[45-49]

Interestingly, meta-analyzing available evidence, we recently demonstrated that weight loss is also able to increase T levels proportionately related to the amount of reduction in body weight.[36] In addition, in the same study we observed a weight loss-dependent increase in SHBG, calculated FT (cFT), LH and

follicle stimulating-hormone (FSH) and a reduction in estradiol. However, multiple regression analysis showed that the degree of body weight lost was the best determinant of total T rise (B=2.50±0.98, P=0.029), whereas no effect of estradiol decrease after weight loss on total T was observed.[36] These data confirm that other fat-associated factors, besides estrogens, can be speculated as mediating obesity associated hypogonadism.

The increase in the amount of physical activity should be an essential component of the lifestyle modifications.[45-49] According to World Health Organization recommendations (http://whqlibdoc.who.int/publications/2010/9789241599979_eng.pdf) adults aged 18–64 years should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week, or at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week, or an equivalent combination of moderate- and vigorous-intensity activity. A recent meta-analysis including 47 studies demonstrated that sedentary behavior in adults significantly increased the risk of all-cause mortality, CVD and cancer mortality and incidence as well as T2DM incidence.[50] Interestingly, a recent randomized controlled trial (RCT) showed that resistance training might have an acute effect on T production and clearance rates, while the exercise-induced increases in serum T appeared to come about through decreased metabolic clearance rate of T.[51]

In line with what has been observed for all the aforementioned conditions, lifestyle modification and maintaining an active lifestyle in men resulted in improvement even in ED.[52] A systematic review and meta-analysis of six RCTs evaluating the effect of lifestyle interventions and pharmacotherapy for CV on the severity of ED demonstrated an overall significant improvement in sexual function, which was confirmed even when only trials of lifestyle change interventions (n=4) were considered.[53]

Testosterone therapy

Despite previous evidence, it should be recognized that everyday clinical practice has shown that diet and behavioral therapies often ultimately fail. In fact, from 60% to 86% of weight lost is regained after 3 years and 75%–121% after 5 years.[54] A meta-analysis including 65 primary qualitative studies on the topic of dietary modification challenges encountered by patients with T2DM and/or heart disease reported that common challenges in these subjects include self-discipline, knowledge, coping with everyday stress, negotiating with family members and managing the social significance of food. This report also confirms that despite health care provider recommendations encouraging people at risk to change their diet, many patients find it difficult to modify what they eat.[55]

T is an anabolic hormone and its effects on muscle growth and function are well known. Recently, some observational studies in men with LOH reported substantial weight loss with T substitution.[56-58] Hence, the concept of testosterone supplementation (TS) as a new anti-obesity medication in men with LOH is gaining ground.[14,18,59-61] On the other hand, TS is able to improve sexual function in hypogonadal (total T <12 nM) men.[61,62] Therefore, T could be used in association with lifestyle intervention in hypogonadal men to improve metabolic and sexual outcomes. In this section, the metabolic and sexual effects of TS will be analyzed in greater detail.

TS and metabolic outcomes

The anti-obesity activity of TS in hypogonadal men may be effective because, on the one hand, it reduces abdominal fat accumulation and, on the other, it improves muscle mass and strength, facilitating adherence to exercise regimens designed to combat obesity.[14,18]

Only a few RCTs have evaluated the impact of TS in patients with MetS and T2DM. By meta-analyzing available evidence, we found that TS was associated with a significant reduction of fasting glycemia, HOMA index, triglyceride levels and waist circumference (WC) in patients with MetS.[10] Correspondingly, an improvement of fasting glycemia, HbA1c and triglyceride levels was observed in subjects with T2DM.[10] To further understand the possible role of TS in body composition and glycometabolic profile in hypogonadal men, we more recently performed a meta-analysis of all RCTs comparing the effect of TS on different metabolic endpoints.[63] Overall, 59 trials were included in the study enrolling 3029 and 2049 subjects in the TS and control groups, respectively. No significant modification of body weight, WC and BMI was detected. However, TS was associated with

a significant reduction of fat and with an increase of lean mass as well as with a reduction of fasting glycemia and homeostasis model assessment (HOMA) index (Table 1). Similar results were observed for total cholesterol and triglyceride levels when only RCTs enrolling hypogonadal (total T<12 mol/L) subjects were considered (Table 1). Conversely, no improvement in high density lipoprotein (HDL) cholesterol levels or in either systolic or diastolic blood pressure was observed (Table 1). In addition, the outcomes were better in younger individuals and in those with metabolic diseases.[63] Finally, when the data were analyzed according to the type of T preparation used, no improvement in body composition (both lean and fat mass modification) and glycemic control was observed in those trials using oral T preparations, whereas the use of both transdermal and parenteral preparations were effective with the application of the latter drugs resulting in better outcomes.[63] The observed improvement in glucose metabolism can be ascribed to either increased muscle mass or to decreased fat mass. However, our data suggest that increased muscle mass is most probably responsible for the more favorable glucose metabolism associated with TS. In fact, the positive associations between T levels, glycemia and HOMA-IR index were confirmed in a multivariate model after adjusting for lean, but not fat, mass.[63] Similarly, in an experimental model of MetS-associated hypogonadism, obtained by feeding rabbits a high-fat diet, we demonstrated that T administration was able to dramatically reduce visceral adiposity and, in cultured adipocytes, to increase insulin sensitivity and triglyceride metabolism.[43] Hence, our data show that TS might help hypogonadal individuals in changing body composition, glucose metabolism, and, possibly, weight.

Table 1. Mean difference or mean standardized differences in several clinical parameters after testosterone substitution as derived from meta-analysis of the available evidence (adapted from ref.# 63)

Clinical parameter	Outcome
Body composition	
Weight (kg)	0.43 [-0.54; 1.39]
Body Mass Index (kg/m^2)	-0.66 [-2.66; 1.35]
Waist circumferences (cm)	0.25 [-0.09; 0.58]
Fat mass (standardised mean)	-0.32 [-0.44; -0.19]**
Lean mass (standardised mean)	0.51 [0.37; 0.66]**
Glucose profile	
Fasting glycemia (mM)	-0.34 [-0.51; -0.17]**
HOMA index	-0.80 [-1.16; -0.45]**
Lipid profile	
Total cholesterol (mM)	-0.357 [-0.61; -0.13]**§
Triglycerides (mM)	-0.22 [-0.37; -0.08]*§
HDL cholesterol (mM)	-0.03 [-0.08; 0.01]
Blood pressure	
Systolic blood pressure (mmHg)	0.94 [-1.08; 2.96]
Diastolic blood pressure (mmHg)	0.95 [-0.66; 2.54]

*p<0.05, **p<0.0001; § only studies enrolling hypogonadal (total testosterone <12 nM) subjects were considered. HDL: high density lipoprotein; RCT: randomized controlled trial.

Considering the positive action of TS on body composition, and in particular on muscle mass and strength, it is possible that in established hypogonadal obese men, combining the effect of TS with lifestyle modifications could result in better outcomes. So far, five RCTs[64-68] have specifically evaluated the effect of a combined therapy with TS and lifestyle modification on HG-associated metabolic derangements and body composition. Overall, the available RCTs enrolled 243 patients, with a mean follow-up of 36.8 weeks. By meta-analyzing these subjects we recently reported that the combination of TS and lifestyle modifications is able to produce better outcomes than lifestyle behaviors alone, including the improvement of body composition (reduction of WC and fat mass and increase in lean mass), lipid profile (reduction of triglycerides levels), insulin resistance (reduction of insulin levels and HOMA index) and diastolic blood pressure (Table 2).[18]

TS and sexual function

The effects of TS on male sexual functions in ED subjects are still very controversial.[69,70] Another controversial issue is the effect of TS on phosphodiesterase type 5 (PDE5) inhibitor (PDE5i) outcomes.[70-72] A substantial improvement in the response to PDE5is was seen in 37.5–92% of these men following a combination of T therapy with PDE5is.[70-72] However, data on placebo controlled RCTs are more conflicting.[73-76]

We recently reported the largest, updated meta-analysis evaluating the effect of TS on male sexual function and its synergism with the use of PDE5is in RCTs comparing the effect of TS vs. placebo or the

Table 2. Mean difference or mean standardized differences in several clinical parameters across randomized controlled trials evaluating the effect of testosterone substitution alone or in combination with low calorie diet and/or physical exercise. Data are presented as derived from the non-paired analysis (adapted from ref.# 18)

Clinical parameter	Outcome
Body composition	
Waist circumferences (cm)	-7.11 [-11.12; -3.11]**
Fat mass (standardised mean)	-1.24 [-2.31; -0.17]*
Lean mass (standardised mean)	1.47 [0.81; 2.13]**
Glucose profile	
Fasting glycemia (mM)	-7.51 [-13.19; -1.83]*
HOMA index	-1.80 [-3.31; -0.29]*
Lipid profile	
Triglycerides (mM)	-0.37 [-0.68; -0.06]*
Blood pressure	
Diastolic blood pressure (mmHg)	-1.53 [-2.48; -0.57]**

*p<0.05, **p<0.0001.

Table 3. Effect size (with 95% confidence interval [CI]) in several sexual parameters across randomized controlled trials evaluating the effect of testosterone substitution vs. placebo (adapted from ref.# 62)

Sexual parameter	Outcome
Erectile function component	
Overall erectile function component§	0.82 [0.47; 1.17]*
Overall sexual-related function component§§	0.75 [0.37; 1.12]**
Sleep-related erections	0.87 [0.47; 1.27]**
Libido component	
Overall libido component	0.81 [0.47; 1.17]**
Orgasm component	
Overall orgasmic component	0.68 [0.34; 1.02]**
Other sexual parameters	
Frequency of intercourse	0.75 [0.33; 1.16]**
Overall sexual satisfaction	0.80 [0.41; 1.20]**
Overall sexual function	0.67 [0.22; 1.12]**

*p<0.001, **p<0.0001. § including coital and non coital erections; §§ only coital erections considered.

effect of TS as an add-on to PDE5is.[62] Overall, 41 RCTs were included in the study, of which 29 compared TS vs. placebo, while 12 trials evaluated the effect of TS as an add-on to PDE5is. Our data clearly indicated that TS is able to significantly ameliorate erectile function and to improve, in hypogonadal men (TT <12 nM), other aspects of male sexual response, including sexual desire and orgasm, as well as several other sexual parameters, including nocturnal erection, frequency of intercourse, overall sexual satisfaction and overall sexual function (Table 3).

Our study, however, was not able to clarify the role of TS as an add-on to PDE5is in the treatment of ED subjects. In fact, although a positive effect was observed in uncontrolled studies, the results were not confirmed when only RCTs were considered. The lack of benefits in RCTs may suggest the uselessness of TS as an adjunctive therapy to PDE5is in ED patients. However, it should be recognized that 3 out of 5[73-75] of the aforementioned RCTs enrolled a population of mixed eugonadal/hypogonadal subjects at baseline. In addition, in Spitzer's large trial,[76] although only hypogonadal subjects were enrolled at baseline, TS was initiated after a sildenafil alone run-in period, leading to T increase up to the normal range (about 12.0 nmol/L). Similarly, it has previously been reported that sexual inertia is associated with functional hypogonadotropic hypogonadism which can be restored accompanied by improvement of sexual activity.[77-81]

CONCLUSION

Hypogonadism represents one of the several complications of obesity and T2DM in men. In these men, hypogonadism can further worsen the metabolic profile and increase abdominal fat. Sexual symptoms are the most specific symptoms associated with hypogonadism in aging men. Although hypogonadism can exacerbate obesity-associated ED, recent data suggest that a direct contribution of fat derived factors could be hypothesized. Lifestyle modifications and weight loss are the first steps for ED patients with obesity or metabolic diseases. In symptomatic hypogonadal men with metabolic impairment and obesity, combining the effect of testosterone substitution with lifestyle modifications could result in better outcomes.

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